Modifying atherosclerosis in cardiometabolic disease: targeting inflammation

Peter Libby
Brigham & Women’s Hospital
Harvard Medical School

Primary Care Congress for Cardiometabolic Health
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Visceral Adipose Tissue (cm²)

Waist girth (cm)

C-Reactive Protein Quintiles


ATP III Metabolic Syndrome Criteria

Diagnosing Metabolic Syndrome
Three of these five criteria must be met:
- Fasting glucose: ≥110 mg/dL
- Triglycerides: ≥150 mg/dL
- Blood pressure: ≥130/85 mm Hg
- High-density lipoprotein cholesterol:
  - Below 50 mg/dL in women, below 40 mg/dL in men.
- Central obesity:
  - Abdominal circumference greater than 35 inches in women, greater than 40 inches in men.

Measurement for waist circumference

Source: National Cholesterol Education Program

Obesity is An Inflammatory Stimulus

Inflammation Drives Diabetes
Elevated Levels of CRP Predict Development of Type 2 Diabetes in the Women’s Health Study

Adjusted Relative Risk for Diabetes*

P=0.001

Quartile of C-reactive protein (CRP)

Ridker Circulation 1003;107-139

Inflammation in the Metabolic Syndrome


History of Discovery

Inflammation in Atherosclerosis

Peter Libby

Abstract—Experimental work has elucidated molecular and cellular pathways of inflammation that promote atherosclerosis. Understanding the role of cytokines as inflammatory messengers provided a mechanism whereby risk factors for atherosclerosis abnormal biology, and produced a systemic model that forms atherosclerotic lesions. The discovery of the immune basis of atherosclerosis demonstrated that inflammation per se was an integral component of the disease, even in the absence of traditional risk factors. Inflammation underlies aspects of plaque biology that trigger the thrombotic complications of atherosclerosis. Translation of these discoveries to human clinical medicine remains a high priority in both basic science research and practical clinical advances. (Arterioscler Thromb Vasc Biol. 2002;22:2645-2651.)

*Adjusted for BMI, family history of diabetes, smoking, physical activity, alcohol consumption, hormone therapy.
Monocyte/Macrophage Heterogeneity in Atherosclerosis

Hyperlipidemia markedly expands circulating inflammatory monocytes in mice

Myeloid cells accumulate in the splenic red pulp in hypercholesterolemic mice

Identification of Splenic Reservoir Monocytes and Their Deployment to Inflammatory Sites

Mononuclear Phagocyte Heterogeneity in Atherosclerosis


CD11b (myeloid cells)
Do new insights into plaque inflammation have clinical implications?

Hypothesis:
An echo in the arterial wall of the inflammation due to acute myocardial infarction aggravates atherosclerosis

Interleukin-1 gene expression in rabbit vascular tissue in vivo

Interleukin-1 α and β mRNA in aortic tissue 2 hours after intravenous injection of 10 μg/kg of E. coli endotoxin in rabbits provided RNA for Northern analysis for rabbit IL-1α and IL-1β. The data presented represent one rabbit per treatment group. Similar results were observed for three additional rabbits per treatment.

Atherogenic diets enhance endotoxin-stimulated interleukin-1 and tumor necrosis factor gene expression in rabbit aortae


The “echo” phenomenon: A systemic inflammatory stimulus, intravenous endotoxin, evokes a local cytokine response in arteries dependent on the amount of pre-existing atherosclerosis


Infectious agents by systemic and local effects can activate artery wall cells


Myocardial infarction accelerates atherosclerosis

During progression of atherosclerosis, systemic cells activate high-risk plaques in the arterial wall and cause their rupture. This triggers myocardial infarction and death. Both the atherosclerotic lesion and death are common causes of death. Myocardial infarction, or MI, occurs when blood flow to a region of the heart is blocked. This can be caused by plaque rupture, which can lead to a clot forming and blocking blood flow. MI enhances protease activity in plaque

MI enhances pro-inflammatory monocytes in plaque

Post MI plaque necrotic cores enlarge and fibrous caps thin

Increased progenitor numbers in spleen after MI

Increased splenic progenitor proliferation in patients after MI

MI enhances atherosclerosis
Can we translate inflammation biology in atherosclerosis to the clinic?

Can Targeted Anti-Inflammatory Therapy Reduce Cardiovascular Event Rates and Prolong Life?

Cardiovascular Inflammation Reduction Trial (CIRT)

Issues in the Selection of Anti-inflammatory Agents for Trials of Cardiovascular Inflammation Inhibition

Ridker, Thromb Haemost 2009
Issues in the Selection of Anti-inflammatory Agents for Trials of Cardiovascular Inflammation Inhibition

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<th>IL-6 inhibition</th>
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Cardiovascular Inflammation Reduction Trial (CIRT)

A randomized, double-blind, placebo-controlled, event-driven trial of weekly low-dose methotrexate (LDM) in the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with type 2 diabetes or metabolic syndrome

BWH/HMS - P. Ridker (PI), R. Glynn (DCC)

NHLBI – A. Hasan, D. Gordon

Methotrexate (MTX) Inhibits Atherogenesis in Cholesterol-Fed Rabbits

MTX

Control

Hematoxylin-eosin

VSMC

Macrophages

MMP-9

Bulgarelli et al, J Cardiovasc Pharmacol 2012;59:308-14

MTX Inhibits Atherogenesis in Cholesterol-Fed Rabbits

No change

MTX

Control

Bulgarelli et al, J Cardiovasc Pharmacol 2012;59:308-14

LDM and CVD: Observational Evidence
To test directly the inflammatory hypothesis of atherothrombosis by evaluating in a randomized, double-blind, placebo-controlled trial whether LDM given at a target dose of 15 mg po weekly over a three to four year period will reduce rates of recurrent myocardial infarction, stroke, or cardiovascular death among patients with previous myocardial infarction and either type 2 diabetes or metabolic syndrome.

**Cardiovascular Inflammation Reduction Trial (CIRT)**

**Primary Aims**

To determine in a randomized, double-blind, placebo-controlled setting whether LDM will reduce the rate of new onset type 2 diabetes among those with metabolic syndrome but not diabetes at study entry.

**Issues in the Selection of Anti-inflammatory Agents for Trials of Cardiovascular Inflammation Inhibition**

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Endotoxin and tumor necrosis factor induce interleukin-1 gene expression in adult human vascular endothelial cells

**Interleukin-1 Induces Interleukin-1: an auto-amplification loop**


Pro-inflammatory actions of IL-1 \( \beta \)

♥ IL-1 induces IL-6 production, a key mediator of the acute phase response


Interleukin-1 Induces Interleukin-6: another amplification loop

IL-1

IL-6


Inflammatory Pathways in Atherogenesis

Pro-Inflammatory Risk Factors

Primary Pro-Inflammatory Cytokines (e.g., IL-1, TNF-\( \alpha \))

IL-6

"Messenger" Cytokine

Endothelium and other cells

CRP

SAA

Liver

ICAM-1

Selectins, HSPs, etc.

Circulation


Interleukin-1: A Signature Cytokine of Innate Immunity

♥ IL-1 \( \beta \) is synthesized as inactive precursor

♥ Limited proteolysis by IL-1 \( \beta \) converting enzyme (caspase 1) activates IL-1 \( \beta \)

Caspase 1 activates IL-1 \( \beta \)

Pro-IL-1\( \beta \) (33 kD)

Caspase 1

( IL-1 \( \beta \) converting enzyme, ICE)

Active IL-1\( \beta \) (17 kD)
Caspase 1 in Human Atheromata

Evidence for Apoptosis in Advanced Human Atheroma
Colocalization with Interleukin-1β-Converting Enzyme

Yong-Jan Geng and Peter Libby
From the Vascular Medicine and Atherosclerosis Unit, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts


The T-cell-Derived Cytokine CD-40L Stimulates Vascular Cells to Produce Active IL-1β

Ligation of CD40 Activates Interleukin 1β-converting Enzyme (Caspase-1) Activity in Vascular Smooth Muscle and Endothelial Cells and Promotes Elaboration of Active Interleukin 1β

Caspase 1 (IL-1β converting enzyme, ICE) in Human Plaque


NLRP3: a Genetic Determinant of Plasma CRP Level

Dehgman et al, Circulation 2011;123:731-8

NLRP3 Cryopyrin Inflammasome, Caspase-1, and IL-1β Maturation
Endogenous Danger Signals in Vascular Biology?


The Inflammasome

activates caspase-1 and hence formation of mature IL-1β

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**LETTERS**

**NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals**


**Cholesterol Crystals Activate the NLRP3 Inflammasome in Human Macrophages: A Novel Link between Cholesterol Metabolism and Inflammation**


**Lipid-laden foam cells**

**Cholesterol Crystals in Atheromata**


**IL-1: Potential Roles in Atherogenesis and Methods of Inhibition**

Adapted from Fearon W. Fearon D. Circulation 2008;117:2077-9
Canakinumab (Ilaris, Novartis)

• high-affinity human monoclonal anti-human interleukin-1β (IL-1β) antibody currently indicated for the treatment of IL-1β driven inflammatory diseases (Cryopyrin-Associated Period Syndrome [CAPS], Muckle-Wells Syndrome)

• designed to bind to human IL-1β and functionally neutralize the bioactivity of this pro-inflammatory cytokine

• long half-life (4-8 weeks) with CRP and IL-6 reduction for up to 3 months

Dose Response of Canakinumab on Plasma IL-6, hsCRP, and fibrinogen: Phase II data

Effects of Interleukin-1β Inhibition With Canakinumab on Hemoglobin A1c, Lipids, C-Reactive Protein, Interleukin-6, and Fibrinogen: A Phase II Randomized, Placebo-Controlled Trial. Ridker, Howard, Walter, Everett, Libby, Hansen and Thuren. Circulation. 2012;126:2739-2748

CANTOS: a 17,200 person phase III Trial

Am Heart J 2011;162:597-605

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

• To test directly the inflammatory hypothesis of atherothrombosis

• To determine whether long-term inhibition of interleukin-1β with canakinumab (50 mg, 150 mg or 300 mg SQ every three months) as compared to placebo will reduce rates of recurrent cardiovascular events among stable post-myocardial infarction patients who remain at elevated vascular risk due to increased levels of hsCRP (> 2 mg/L) despite usual care, including statin therapy.
IL-1 beta Antagonism

♥ CANTOS provides an exciting opportunity to
♥ Test the inflammatory hypothesis of atherosclerosis
♥ Provide a novel therapy to address residual risk in secondary prevention

Inflammation, Atherothrombosis, and Cardiovascular Prevention: Three Key Translational Questions

Do individuals with elevated levels of inflammatory biomarkers have high cardiovascular risk even when other risk factors are acceptable? Yes

Do individuals identified at increased risk due to inflammation benefit from a therapy they otherwise would not have received? JUPITER – Yes

Is there evidence that reducing inflammation per se will reduce vascular events and slow progression of diabetes? CIRT, CANTOS – Let’s find out

P. Ridker

With Appreciation

National Heart Lung and Blood Institute
National Cancer Institute
American Heart Association
Doris Duke Charitable Foundation
Foundation Leducq
Donald W Reynolds Foundation

Dade Behring / Siemens
Bristol Myers Squibb
Amgen / Illumina
AstraZeneca
Novartis

For More Information: 1-855-437-9330
theCIRT.org theCANTOS.org

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